

were most appreciated. The substance of the interview will be clear from the discussion presented below.

II. THE OBVIOUSNESS REJECTION

(a) The Examiner's Position

Claims 3-9, 11-16, 18-19, 21-25 and 35-36 have been rejected under 35 USC 103 as unpatentable over Wicha et al, reference AR (hereinafter Wicha). This is the only outstanding rejection in the case. The Examiner's position is that Wicha renders obvious the claims of the present case by teaching a compound which embraces applicants' claimed compounds, specifically compound 11 appearing on page 21 of Wicha. The Examiner correctly notes that compound 11 has been excluded from the claims for anticipation purposes, but nevertheless takes the position that the present compounds are structural homologs of compound 11. From this, the Examiner has concluded that one having ordinary skill in the art would have been motivated to prepare the presently claimed invention because such structurally homologous compounds would be expected to possess similar properties. The Examiner specifically states that:

"It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950)".

The Examiner has concluded that the compounds of present invention are obvious with respect to Wicha intermediate compound 11 since the intermediate is isolated by the reference and is structurally related to a product having physiological activity. The Examiner takes the position that the applicants have the burden of establishing that the claimed invention has unexpected results over the prior art Wicha compound 11.

The rejection is traversed for the following reasons.

(b) The Invention

The present invention is directed to a selected class of 17-pyridyl steroids which act as hydroxylase-lyase inhibitors. The present inventors have discovered, surprisingly, that hydroxylase-lyase inhibitory activity is possessed only when:

- (1) the nitrogen atom of the pyridyl ring is in the 3- (or meta) position relative to the point of attachment of the pyridyl ring to the steroid residue, and
- (2) when the steroid molecule possesses 16,17-unsaturation.

The claims in the case are directed to steroids *per se* possessing the above structural features, compositions containing the steroids, and a method of using the steroids to treat androgen-dependent and estrogen-dependent disorders, especially prostatic cancer and breast cancer. Claims to the preparation of the steroids are the subject of copending application Serial No. 08/392,178, filed February 22, 1995.

The compounds as claimed in claim 35 are novel. As noted during the interview, certain compounds have been disclosed as **intermediates** in the synthesis of certain steroids having a 3-pyridyl or a 3-pyridonyl group in the 17 β -position, and those compounds are excluded from the claims directed to the compounds *per se*.

As discussed in more detail below, Wicha contains no suggestion that such excluded intermediate compounds are useful for treating androgen-dependent or estrogen-dependent disorders. In view of this, the compounds disclosed as intermediates in Wicha have not been excluded from the method of treatment claims 36 and 18-24 or from claim 25 directed to an orally ingestible solid

composition comprising a compound of the invention in association with a pharmaceutically acceptable carrier or diluent.

(c) The Wicha Teaching

Wicha relates to the synthesis of steroids of formula (3) (see page 20) alleged to have "cardiotonic" properties (i.e. able to stimulate the heart by increasing the force of myocardial contraction). The scheme shown on page 21 of AR describes the numerous intermediates involved in the synthesis of compounds of the formula (3), including the compound of formula 11. The structure of the final compounds of formula (3), which allegedly possess cardiotonic activity, bears no resemblance whatsoever to the compounds as claimed in the present application. Thus, the compounds of formula (3) on page 20 of Wicha possess:

- (1) a 14 β -hydroxy substituent, and
- (2) NO unsaturation at the 16,17-position of the D ring.

The presently claimed compounds on the other hand do **not** possess a hydroxyl substituent at the 14-position, and do possess 16,17-unsaturation, unlike the Wicha compounds of formula (3). Wicha has nothing whatsoever to do with the treatment of androgen-dependent or estrogen-dependent disorders, nor with compounds which might possess hydroxylase-lyse activity or be useful in the treatment of such disorders. Wicha therefore fails to suggest to a person of ordinary skill that compounds having the structural features of the presently claimed compounds (a 17-(3-) pyridyl group together with 16,17-unsaturation) would act as hydroxylase-lyase inhibitors and would be useful for the treatment of androgen-dependent and estrogen-dependent disorders. Absent any such suggestion, a person of ordinary skill, seeking compounds which might be useful in the treatment of androgen-dependent and estrogen-dependent disorders, would not have been motivated to follow the Wicha teaching. Certainly, there would have been no

motivation to evaluate the synthesis intermediate compound 11, for which absolutely no pharmacological activity is taught or suggested. Wicha thus fails to give rise to a *prima facie* case of obviousness of the claimed compounds.

(d) Secondary Considerations

Given that there is no *prima facie* case of obviousness, there is no need to rely on secondary considerations, such as comparative evidence, to establish patentability. The applicants have, in fact, provided evidence of unexpected results both in the originally-filed specification and in the form a Rule 132 declaration (the Barrie Declaration). However, while such evidence is convincing, it is not necessary for purposes of establishing patentability. Patentability subsists in the compounds as claimed *per se*, as well as the compositions and method of use, by virtue of their specific structural features and the unexpected pharmaceutical properties arising as a result of those structural features. As regards the method of treatment claims, Wicha is silent with respect to the use of the compounds as now defined for treating androgen-dependent or estrogen-dependent disorders. Clearly, therefore, no *prima facie* case of obviousness arises with respect to the method of treatment claim 36 and claims dependent thereon.

Patentability of the claimed invention is further established by the evidence present in the originally-filed application and that contained in the Barrie declaration submitted with the response of September 11, 1995. **As stated above, since there is no *prima facie* case of obviousness in this case, the applicants do not need to rely on the evidence of record to further substantiate patentability.** For completeness, however, the evidentiary showing contained in the application and the Barrie declaration is summarized below.

Table 1 on page 5 of the specification demonstrates the enzyme inhibitory effect possessed by the presently claimed compounds. In that Table, enzyme activities are measured by IC₅₀ figures, IC₅₀ being the concentration of test

compound required to achieve 50% enzyme inhibition. Thus, the lower the number in the column, the more effective is the test compound. It will be seen that the 3-pyridyl compound is roughly from 40 to 80 more effective than the 2-pyridyl counterpart and 700-1200 times more effective than the 4-pyridyl counterpart.

Table 2 on pages 37-38 of the specification shows that variations in the A, B and C rings of the steroid molecule have little effect on inhibition of hydroxylase and lyase. This evidence further establishes the importance of the structure of the D ring of the steroid molecule to achieving the desired properties, independent of the nature of the A, B and C rings.

The Barrie declaration focuses on the importance of 16,17-unsaturation in the compounds of the invention. The declaration describes tests conducted on a compound within the scope of claim 35 and its D-ring saturated analogue relating to inhibition of the 17 α -hydroxylase-lyase enzyme. Compound (1) in the Table in paragraph 7 of the Barrie declaration is a compound of the invention; compound (2) is its D-ring saturated analogue. As will be seen from the results, the fall-off in inhibitory activity with D-ring saturation is in the region of 10-fold. A comparison is also shown for the corresponding 17-4-(pyridyl) compounds (3) and (4) where the reverse trend is seen, but the 4-pyridyl compound are relatively inactive.

Wicha fails to give rise to a *prima facie* case of structural obviousness, and so the secondary evidence of record, while convincing and commensurate, is not essential to a holding of patentability in this case. The closest prior art compounds are excluded from the claimed invention. Moreover, those closest prior art compounds, including compound 11, are disclosed as **synthesis intermediates**, with no teaching or suggestion that they possess any pharmaceutical utility. There simply would have been no basis or motivation for a person of ordinary skill, seeking a compound possessing the utility exhibited by the present compounds, to stop the Wicha synthesis at intermediate compound 11 and expect the compound to

possess any utility, whether cardiotonic utility or the utility disclosed in the present case.

The **ultimate** compounds which are produced by Wicha using the synthesis intermediates (including intermediate compound 11) are not only structurally remote from the presently claimed compounds but allegedly possess a utility, cardiotonic properties, which is remote from the utility of the present compounds. The enzyme involved with cardiotonic properties (the Na/K-ATPase enzyme) is different to that with which the applicants are concerned (the 17 α -hydroxylase-lyase enzyme). Moreover, as noted during the interview, the response filed in this case on September 11, 1995 contains a discussion beginning at page 3 last line and extending through to page 11 (herein incorporated by reference) of evidence in the form of published literature references which clearly establishes that **BOTH** a 14 β -hydroxy group **AND** 16,17 saturation are essential to achieving cardiotonic properties. Of particular note are references AAE to AAH which show that cardiotonic activity falls off when the 14 β -hydroxy is replaced by a hydrogen atom, and references AAI-AAK which show that cardiotonic activity also falls off when 16,17-unsaturation is introduced into the D-ring. The presently claimed compounds on the other hand do not contain a 14 β -hydroxy group or 16,17-saturation. **Thus, the present compounds in fact contain structural features which the other prior art cited above teaches reduces cardiotonic activity, and are therefore not obvious over the Wicha teaching even for this purpose.**

In summary, a person of ordinary skill would not have been motivated to rely on the Wicha teaching when seeking to solve the problem of developing compounds active as hydroxylase-lyase inhibitors and suitable for use in the treatment of androgen-dependent estrogen-dependent disorders because Wicha focuses on compounds allegedly having cardiotonic properties which involve a different enzyme and requires the presence of structural features not possessed by the presently claimed compounds. Far from there being any motivation to make the intermediate compound of Wicha, there is actually **demotivation**, because the art of

record AAE-AAH and AAI-AAK teaches away from the structure of the compounds of the invention. In view of such demotivation, and indeed absent any motivation, a *prima facie* case of obviousness has clearly not been made out. Reconsideration and withdrawal of the obviousness rejection on this ground alone is accordingly respectfully requested.

(e) The Case Law

The case for patentability of the presently claimed invention is fully supported by decided case law. In particular, during the interview, attention was drawn to the cases of *In re Lahu*, 223 USPQ 1256 (CAFC 1984), as well as other cases in accord (see, for example, *In re Gyurik*, 201 USPQ 552 (CCPA 1979), *In re Stemniski*, 170 USPQ 343 (CCPA 1971), and *In re Magerlein*, 202 USPQ 473 (CCPA 1979)).

The *Lahu* case involved perfluoroalkyl sulfonyl chlorides and bromides useful in the textile, leather and paper industries. The compounds were indicated to have utility as corrosion inhibiting agents, surface active agents and leveling agents and could be incorporated into waxes, greases, varnishes and paints to improve the spreading out and leveling of those viscous products. The cited U.S. patent to Oesterling disclosed certain dihydroperfluoroalkyl sulfonic acids which were prepared by chlorination of the corresponding disulfites to form the corresponding intermediate sulfonyl chlorides, which were then hydrolyzed. The Examiner rejected the *Lahu* claims as obvious on the ground that Oesterling taught homologous halide compounds. The Board affirmed the Examiner's rejection, arguing that the close structural similarity between the reference sulfonyl chlorides compounds and the claimed compounds was sufficient to raise a presumption of obviousness. The court reversed noting that:

"The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications

needed to arrive at the claimed compound. *In re Stemniski* (citations omitted).

In *Stemniski*, the claimed compounds were rejected over structurally closely related compounds disclosed in prior art references. The references did not disclose or suggest any usefulness or significant properties, whereas the applicant disclosed a use for the claimed compounds of his application”.

The court noted that, in such a case, the requisite motivation to make the claimed compound would not be present. The court quoted from the *Stemniski* decision as follows:

“How can there be obviousness of structure, or particularly of the subject matter as a whole, when no apparent purpose or result is to be achieved, no reason or motivation to be satisfied, upon modifying the reference compounds’ structure? Where the prior art reference neither discloses nor suggests a utility for certain described compounds, why should it be said that a reference makes obvious to one of ordinary skill in the art an isomer, homolog of related structure, when that mythical, but intensely practical, person knows of no “practical” reason to make the referenced compounds, much less any structurally related compounds?”.

In *Lalu*, the Board had argued that the disclosed utility for the Oesterling sulfonyl chlorides as an **intermediate** for producing useful acids was a usefulness conforming with statutory guidelines. However, the court noted that the cases relied upon by the Board in support of that contention were inapposite. The court went on to review other cases involving obviousness which dealt with the role of intermediates and cited, in particular, the case of *In re Gyurik*, mentioned above. The court noted that the *Gyurik* court stressed that, in obviousness rejections based on close similarity in chemical structure, the necessary motivation to make a claimed compound, and thus the *prima facie* case of obviousness, rises from the expectation that compounds similar in structure would have similar properties. The court in *Gyurik* stated that “no common-properties presumption rises” from the

mere occurrence of a claimed compound at an intermediate point in a conventional reaction yielding a specifically named prior art compound. The *Gyurik* court further stated:

“That an intermediate/end-product relationship exists between a claimed compound and a prior art compound does not alone *create a common-properties presumption*. Absent that presumption or other evidence of motivation, it cannot be said that it would have been obvious to stop the process for synthesizing the disclosed end-product and isolate the claimed intermediate” (citations omitted; emphasis in the original).

It was further stated in the *Gyurik* decision that the mere ability of a compound to act as an intermediate toward the production of other compounds does not alone constitute the sort of “property” that the cases on obviousness of chemical compounds contemplated. From the above, the court in *Lalu* concluded:

“There is no disclosure that the Oesterling compounds would have any properties in common with those of appellants’ compounds, as those properties of the former relate to the use of the compounds for base neutralization, catalysis, metal cleaning and fuel. The mere fact that Oesterling’s sulfonyl chlorides can be used as an intermediates in the production of the corresponding sulfonic acids does not provide other motivation for one of ordinary skill in the art to stop the Oesterling synthesis and investigate the intermediate sulfonyl chlorides with the expectation of arriving at appellants’ claimed halides for use as corrosion inhibiting agents, surface active agents, or leveling agents”.

The case of *In re Stemniski* related to lubricant compositions containing a disubstituted aryloxyaryl tin compound. The Examiner rejected the claims over primary teachings of various diaryl tin compounds and a secondary reference disclosing tetravalent aryl substituted tin compound in which the aryl groups could contain 1 to 3 rings for example biphenyl and phenoxyphenyl (an aryloxyaryl group). The Board affirmed the rejection taking the position that it would have

been obvious to substitute a phenoxyphenyl group for a biphenyl group in the prior art diaryl tin compounds. The Board opined that the fact that the compounds of the secondary art were tetravalent tin compounds was not significant as a teaching to the chemist of equivalence of the substituent groups. The court reversed, noting that it could **not** be assumed that the properties of the two set of compounds would be substantially the same because of the close structural similarity of the compounds. The court observed that there was "arguable precedent" for the Patent Office position in the case of *In re Henze*. Later, in the *Stemniski* decision, the court specifically overruled *Henze* to the extent that it was inconsistent with its decision.

(f) Application of Case Law to the Present Application

The Examiner's position that Wicha renders obvious the claims of the present case in view of the teaching of intermediate compound 11 is clearly at odds with the decided case law, especially *Lalu*. In particular, the Examiner's reliance on the *Henze* decision is of no effect, since that case has been overruled. Moreover, as confirmed by *Lalu*, there is no "common-properties presumption" arising from the fact that a compound as claimed appears as an intermediate point in a reaction. *Lalu* makes it clear that the mere existence of an intermediate/end-product relationship between a claimed compound and a prior art compound does not alone create a common-properties presumption. The Examiner's statement on page 3, therefore, that one having ordinary skill in the art would have been motivated to prepare the instantly claimed invention because the structurally homologous compounds are expected to possess similar properties is contrary to the decided case law.

A critical structural feature of the Wicha final compounds is that they possess 16,17-saturation. As described on page 21 of Wicha, intermediate compound 11 is reduced with hydrogen over palladium on charcoal in THF to furnish the required product 14. In this reduction, the 16,17-unsaturation is

removed in order to produce the final 16,17 saturated steroids. On the basis of this teaching, there would have been no motivation for one of ordinary skill in the art to stop the Wicha synthesis and investigate the intermediate 16,17-unsaturated intermediates with an expectation of arriving at the presently claimed steroids having useful properties in an area remote from even the therapeutic activity of the final Wicha.

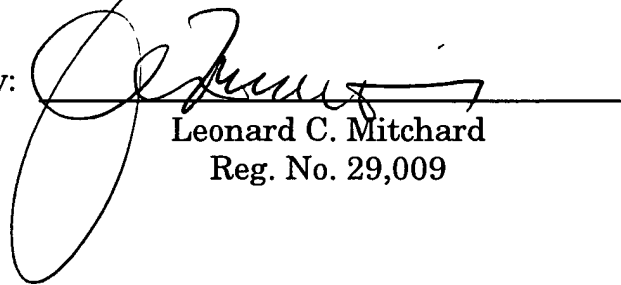
For all of the above reasons, reconsideration and withdrawal of the outstanding obviousness rejection is in order. Such action is respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

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